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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/082,018	02/20/2002	Li How Chen	10275-133002 / GTC-39C US	8070

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GTC BIOTHERAPEUTICS, INC.
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EXAMINER	
CROUCH, DEBORAH	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/082,018	CHEN ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,13-15,17-20,24-26,28-30,35-38,40-42,47-50,52-55,59-61,63-66,70-72 and 74-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Cont Sheet

J.D.O

Continuation of Disposition of Claims: Claims pending in the application are 9,13-15,17-20,24-26,28-30,35-38,40-42,47-50,52-55,59-61,63-66,70-72 and 74-76.

An examiner's amendment to the record appears below. Authorization for this examiner's amendment was given in a telephone interview with Mr. Byron Olsen on July 29, 2005. These claims are now entered and the claims of record. This office action and responses to this office action are with regard to these claims.

1. Rewrite the claims as follows.

55. A non-human transgenic mammal whose genome comprises a modified SEQ ID NO. 2 encoding wild type MSP-1 operably linked to a mammary gland promoter, wherein the modification reduces the AT content of SEQ ID NO: 2 by 50% or less by replacement of protozoan codons with codons preferred by mammalian cells, wherein the replacement codons encode the same amino acid as the replaced codon, and wherein the transgenic mammal expresses said modified SEQ ID NO: 2, thereby to produce MSP-I in its milk.

60. The method of claim 55, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid sequence that lacks at least one glycosylation site.

61. The method of claim 60, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid sequence that lacks all glycosylation sites.

63. The method of claim 55, wherein modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid substitution at position 181.

64. The method of claim 55, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid substitution at position 262.

65. The method of claim 55, wherein the modified SEQ ID NO: 2 encodes MSP-1 comprising amino acid substitutions at positions 181 and 262.

9. A method of producing a merozite surface protein 1 (MSP-I) in the milk of a non-human transgenic mammal, comprising:

providing a non-human transgenic mammal whose genome comprises a modified SEQ ID NO. 2 encoding wild type MSP-1 operably linked to a mammary gland promoter,

wherein the modification reduces the AT content of SEQ ID NO: 2 by 50% or less by replacement of protozoan codons with codons preferred by mammalian cells, wherein the replacement codons encode the same amino acid as the replaced codon; and

allowing the transgenic mammal to express said modified SEQ ID NO: 2, thereby to produce MSP-I in its milk.

14. The method of claim 9, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid sequence that lacks at least one glycosylation site.

15. The method of claim 14, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid sequence that lacks all glycosylation sites.

17. The method of claim 9, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid substitution at position 181.

18. The method of claim 9, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid substitution at position 262.

19. The method of claim 9, wherein the modified SEQ ID NO: 2 encodes MSP-1 comprising amino acid substitutions at positions 181 and 262.

66. A non-human transgenic mammal whose genome comprises a modified SEQ ID NO. 2 encoding a wild-type MSP-I operably linked to a mammary gland promoter, wherein the modification eliminates all the mRNA instability motifs in said SEQ ID NO: 2 by replacement of protozoan codons with codons preferred by mammalian cells, wherein the replacement codons encode the same amino acid as the replaced codon, and wherein the transgenic mammal expresses said modified SEQ ID NO: 2, to thereby produce MSP-I in its milk.

71. The method of claim 66, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid sequence that lacks at least one glycosylation site.

72. The method of claim 71, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid sequence that lacks all glycosylation sites.

74. The method of claim 66, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid substitution at position 181.

75. The method of claim 66, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid substitution at position 262.

76. The method of claim 66, wherein the modified SEQ ID NO: 2 encodes MSP-1 comprising amino acid substitutions at positions 181 and 262.

20. A method of producing a merozite surface protein 1 (MSP-I) sequence in the milk of a non-human transgenic mammal, comprising:

providing a non-human transgenic mammal whose genome comprises a modified SEQ ID NO. 2 encoding a wild-type MSP-I operably linked to a mammary gland promoter, wherein the modification eliminates all the mRNA instability motifs in said SEQ ID NO: 2 by replacement of protozoan codons with codons preferred by mammalian cells, and wherein the replacement codons encode the same amino acid as the replaced codon; and

allowing the transgenic mammal to express said modified SEQ ID NO: 2, to thereby produce MSP-I in its milk.

25. The method of claim 20, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid sequence that lacks at least one glycosylation site.

26. The method of claim 25, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid sequence that lacks all glycosylation sites.

28. The method of claim 20, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid substitution at position 181.

29. The method of claim 20, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid substitution at position 262.

42. A transgenic non-human mammal whose genome comprises a modified SEQ ID NO. 2 encoding a wild-type MSP-I operably linked to mammary gland specific promoter, wherein

the modification eliminates all the mRNA instability motifs of said SEQ ID NO: 2 by replacement of one or more protozoan codons with codons preferred by mammalian cells and the modification reduces the AT content of said SEQ ID NO: 2 by 50% or less by replacement of protozoan codons with codons preferred by mammalian cells, wherein the replacement codons encode the same amino acid as the replaced codon and wherein the transgenic mammal expresses said modified SEQ ID NO: 2, thereby to produce MSP-1 in its milk.

47. The method of claim 42, wherein the modified SEQ ID NO: 2 is expressed in milk at a level which is at least 25% more than the wild-type sequence is expressed under the same conditions.

48. The method of claim 42, wherein the modified SEQ ID NO: 2 is expressed in milk at a level which is at least 50% more than the wild-type nucleic acid sequence is expressed under the same conditions.

49. The method of claim 42, wherein the modified SEQ ID NO: 2 is expressed in milk at a level which is at least 100% more than the wild-type nucleic acid sequence is expressed under the same conditions.

50. The method of claim 42, wherein all protozoan codons are replaced with codons preferred by mammalian cells.

52. The method of claim 42, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid substitution at position 181.

53. The method of claim 42, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid substitution at position 262.

30. A method for producing a merozite surface protein 1 (MSP- 1) sequence in the milk of a non-human transgenic mammal, comprising:

providing a non-human transgenic mammal whose genome comprises a modified SEQ ID NO. 2 encoding a wild-type MSP-I operably linked to a mammary gland promoter, wherein the nucleic acid has been modified by

a) elimination of mRNA instability motifs by the replacement of protozoan codons in SEQ ID NO: 2 with codons preferred by mammalian cells; and

b) reduction of AT content by 50% or less by the replacement of one or more AT-containing protozoan codons of SEQ ID NO: 2 with codons preferred by mammalian cells,

wherein the replacement codons encode the same amino acid as the replaced codon; and

allowing the transgenic mammal to express said modified SEQ ID NO: 2, to thereby produce MSP-I in its milk.

35. The method of claim 30, wherein the modified SEQ ID NO: 2 is expressed in milk at a level which is at least 25% more than the wild-type sequence is expressed under the same conditions.

36. The method of claim 30, wherein the modified SEQ ID NO: 2 is expressed in milk at a level which is at least 50% more than the wild-type nucleic acid sequence is expressed under the same conditions.

37. The method of claim 30, wherein the modified SEQ ID NO: 2 is expressed in milk at a level which is at least 100% more than the wild-type nucleic acid sequence is expressed under the same conditions.

38. The method of claim 30, wherein all protozoan codons are replaced with codons preferred by mammalian cells.

40. The method of claim 30, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid substitution at position 181.

41. The method of claim 30, wherein the modified SEQ ID NO: 2 encodes an MSP-1 comprising an amino acid substitution at position 262.

2. Cancel claim 73.

3, Add the following claim:

42. The method of claim 30, wherein the promoter is a beta casein promoter.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 9, 13-15, 17-20, 24-26, 28, 29, 30, 35-38, 40-42, 47-50, 52-55, 59-61, 63-66, 70-72 and 74-76 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 85-92 of copending Application No. 09/175,683. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are encompassed by claims 85-92 in '683.

The present claims are to methods for producing a merozite surface protein 1 (MSP-1) sequence in the milk of a non-human transgenic mammal, where SEQ ID NO: 2, encoding MSP-1, has been modified to replace protozoan codons with those preferred by mammalian cells to decrease the number of AT's and/or decrease mRNA instability motifs,

and the mammal. Claims 85-92 of '683 claim methods for producing MSP-1 in the milk of a nonhuman mammal comprising the same modifications in a nucleic acid sequence encoding MSP-1, and the mammal. The specification of '683 discloses MSP-1 to be encoded by SEQ ID NO: 2. Thus, given the claims in '683, it would have been obvious to the ordinary artisan at the time of filing to reach the presently claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

August 8, 2005